A landscape of germ line mutations in a cohort of inherited bone marrow failure patients

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Résumé en anglais	Bone marrow (BM) failure (BMF) in children and young adults is often suspected to be inherited, but in many cases diagnosis remains uncertain. We studied a cohort of 179 patients (from 173 families) with BMF of suspected inherited origin but unresolved diagnosis after medical evaluation and Fanconi anemia exclusion. All patients had cytopenias, and 12.0% presented ≥5% BM blast cells. Median age at genetic evaluation was 11 years; 20.7% of patients were aged ≤2 years and 36.9% were ≥18 years. We analyzed genomic DNA from skin fibroblasts using whole-exome sequencing, and were able to assign a causal or likely causal germ line mutation in 86 patients (48.0%), involving a total of 28 genes. These included genes in familial hematopoietic disorders (,), telomeropathies (, ,), ribosome disorders (, ,), and DNA repair deficiency (). Many patients had an atypical presentation, and the mutated gene was often not clinically suspected. We also found mutations in genes seldom reported in inherited BMF (IBMF), such as and (N = 16 of the 86 patients, 18.6%), (N = 6, 7.0%), and (N = 7, 8.1%), each of which was associated with a distinct natural history; and patients often experienced transient aplasia and monosomy 7, whereas patients presented early-onset severe aplastic anemia, and patients, mild pancytopenia with myelodysplasia. This study broadens the molecular and clinical portrait of IBMF syndromes and sheds light on newly recognized disease entities. Using a high-throughput sequencing screen to implement precision medicine at diagnosis can improve patient management and family counseling.
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